8 ANSWER 8 OF 15 MEDLINE
AN 94284045 MEDLINE
DN 94284045 PubMed ID: 7516926
TI **Melanoma**-specific **CD4+** T lymphocytes recognize human **melanoma** antigens processed and presented by Epstein-Barr virus-transformed B cells.
AU Topalian S L; Rivoltini L; Mancini M; Ng J; Hartzman R J; Rosenberg S A
CS Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.
SO INTERNATIONAL JOURNAL OF CANCER, **(1994 Jul 1)** 58 (1) 69-79.
Journal code: GQU; 0042124. ISSN: 0020-7136.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199407
ED Entered STN: 19940810
Last Updated on STN: 19970203
Entered Medline: 19940726
AB While much emphasis has been placed on the role of **MHC** class I-restricted CD8+ T cells in the recognition of tumor-specific antigens (Ag), evidence has accumulated that **CD4+** T cells also play a critical role in the anti-tumor immune response. However, little information exists on the nature of **MHC** class II-restricted human tumor Ag. In an attempt to develop in vitro systems to characterize such Ag, we examined the ability of Epstein-Barr virus (EBV)-transformed B cells to present **melanoma**-associated Ag to **melanoma** -specific **CD4+** cells. **CD4+** T cells cultured from lymphocytes infiltrating a s.c. **melanoma** metastasis secreted TNF-alpha and GM-CSF specifically in response to autologous cultured **melanoma** cells expressing **MHC** class II molecules. These **CD4+** cells also recognized **MHC** class II-compatible EBV-B cells pulsed with extracts of autologous **melanoma** cells, but failed to recognize EBV-B cells pulsed with autologous non-transformed cells or a variety of allogeneic tumors or normal cells. B cells pre-fixed with paraformaldehyde were incapable of Ag presentation, suggesting that intracellular processing events were occurring. Antibody-blocking studies defined **HLA-DR** as the dominant if not exclusive restriction locus in this T-B interaction, and **HLA-DR** genotyping revealed DRBI*0404 to be the probable restriction element. In a second patient, a **CD4+** T-cell clone cultured from a **melanoma** lesion recognized autologous tumor Ag presented by autologous EBV-B; no corss-reactivity was observed with the other tumor system investigated, nor with autologous **CD4+** T cells specific for tetanus toxoid. These findings demonstrate that tumor Ag can be processed and presented by EBV-transformed B cells to **MHC** class II-restricted tumor-specific **CD4+** T cells. They also provide a model system for direct identification of these tumor-derived antigens.

L8 ANSWER 6 OF 15 MEDLINE
AN 95023931 MEDLINE
DN 95023931 PubMed ID: 7937789
TI Human **CD4**+ T cells specifically recognize a shared **melanoma**-associated antigen encoded by the **tyrosinase** gene.
AU Topalian S L; Rivoltini L; Mancini M; Markus N R; Robbins P F; Kawakami Y;
Rosenberg S A
CS Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1994 Sep 27)** 91 (20) 9461-5.
Journal code: PV3; 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199410
ED Entered STN: 19941222
Last Updated on STN: 19941222
Entered Medline: 19941027
AB Although commonly expressed human **melanoma**-associated antigens recognized by CD8+ cytolytic T cells have been described, little is known about **CD4**+ T-cell recognition of **melanoma**-associated antigens. Epstein-Barr virus-transformed B cells were used to present antigens derived from whole cell lysates of autologous and allogeneic **melanomas** for recognition by **melanoma**-specific **CD4**+ T-cell lines and clones cultured from tumor-infiltrating lymphocytes. **HLA-DR**-restricted antigens were detected in the lysates on the basis of specific release of cytokines from the responding T cells. Antigen sharing was demonstrated in the majority of **melanomas** tested, as well as in cultured normal melanocytes, but not in other normal tissues or nonmelanoma tumors. T-cell clones manifested a single recognition pattern, suggesting the presence of an immunodominant **epitope**. This **epitope** was identified as a product of the **tyrosinase** gene, which has also been shown to encode class I-restricted **epitopes** recognized by CD8+ T cells from **melanoma** patients. Identification of commonly expressed tumor-associated protein molecules containing **epitopes** presented by both class I and class II major histocompatibility molecules may provide optimal reagents for cancer immunization strategies.

L8 ANSWER 5 OF 15 MEDLINE
AN 95114403 MEDLINE
DN 95114403 PubMed ID: 7814883
TI Reactivity of autologous **CD4+** T lymphocytes against human **melanoma**. Evidence for a shared **melanoma** antigen presented by HLA-DR15.
AU Takahashi T; Chapman P B; Yang S Y; Hara I; Vijayasaradhi S; Houghton A N
CS Immunology Program, Memorial Sloan-Kettering Cancer Center, New York, NY 10021.
NC CA33049 (NCI)
CA58621 (NCI)
SO JOURNAL OF IMMUNOLOGY, **(1995 Jan 15)** 154 (2) 772-9.
Journal code: IFB; 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199502
ED Entered STN: 19950217
Last Updated on STN: 19970203
Entered Medline: 19950209
AB Reactivity of CD8+ T lymphocytes against human **melanoma** has been extensively characterized, but little is known about **melanoma** Ags recognized by **CD4+** lymphocytes. We have identified **CD4+** CTL that recognize shared **melanoma** Ag(s) expressed by autologous **melanoma** cells and a subset of allogeneic **melanomas**. The same Ag(s) was shared by autologous and positive allogeneic **melanomas** by cross-blocking experiments. Cytotoxicity was directed against **epitopes** presented by **HLA-DR** on target **melanoma** cells, and allelic typing revealed that cytotoxicity was restricted through HLA-DR15. These **CD4+** T cells released IFN-gamma, IL-4, and TNF-alpha, but not IL-2, in response to HLA-DR15+ target cells. **CD4+** T cells did not lyse DR15+ nonmelanoma cell types, including melanocytes or fibroblasts (induced to express **HLA-DR** by IFN-gamma). Thus, by cytotoxicity assays, shared Ags were only recognized on **melanoma** cells but not on normal melanocytes. In summary, this analysis shows that **melanoma** cells share an Ag that is presented by HLA-DR15.

L8 ANSWER 3 OF 15 MEDLINE
AN 96020509 MEDLINE
DN 96020509 PubMed ID: 8528947
TI Analysis of cytokine secretion by **melanoma**-specific **CD4** + T lymphocytes.
AU Markus N R; Rosenberg S A; Topalian S L
CS Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.
SO JOURNAL OF INTERFERON AND CYTOKINE RESEARCH, **(1995 Aug)** 15 (8) 739-46.
Journal code: CD4; 9507088. ISSN: 1079-9907.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199601
ED Entered STN: 19960220
Last Updated on STN: 19970203
Entered Medline: 19960129
AB Although specific antitumor immune reactivity has been documented extensively in CD8+ T cells derived from **melanoma** patients, relatively little is known about **CD4**+ T cell responses against **melanoma**. Tumor-infiltrating lymphocytes (TIL) cultured from metastatic lesions in five patients yielded cytolytic CD8+ T cells with specific activity against autologous and **MHC** class I-compatible allogeneic **melanoma** targets. In four of the five cases studied, **CD4**+ T cells purified from bulk TIL cultures also reacted specifically with autologous **melanoma** cells, as manifested by the secretion of various cytokines (GM-CSF, TNF-alpha, and IFN-gamma) after a 24 h cocultivation. Cytokine secretion by **CD4**+ T cells was **MHC** class II restricted, and proved to be a more reliable indicator of the immunologic reactivity of **CD4**+ T cells than cytolysis. Three of the four reactive **CD4**+ TIL failed to recognize allogeneic **melanomas**, suggesting recognition of Ag with limited expression in the patient population. Cloning such Ags may provide clues to optimizing current antitumor immunization strategies.

L8 ANSWER 1 OF 15 MEDLINE
AN 96062017 MEDLINE
DN 96062017 PubMed ID: 7589064
TI HLA class II-restricted recognition of common tumor **epitopes** on human **melanoma** cells by **CD4+ melanoma** -infiltrating lymphocytes.
AU Le Drean E; Gervois N; Diez E; Semana G; Dreno B; Jotereau F
CS Unite INSERM 211, Nantes, France.
SO EUROPEAN JOURNAL OF IMMUNOLOGY, **(1995 Oct)** 25 (10) 2732-6.
Journal code: EN5; 1273201. ISSN: 0014-2980.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199512
ED Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951212
AB **CD4+** T cell clones derived from lymphocytes infiltrating four human **melanomas** specifically recognized **melanoma** -derived tumor **epitopes** as shown by secretion of tumor necrosis factor (TNF) in vitro upon interaction with autologous **melanoma** cells, whereas they did not recognize HLA class II-expressing autologous lymphoblasts or HLA class II mismatched allogeneic **melanoma** cells. Specificity was further established by demonstrating that TNF responses to tumor cells were inhibited by **HLA-DR** or HLA-DQ monoclonal antibodies. Most of these clones cross-reacted with allogeneic **melanoma** cells expressing a potentially restricting HLA allele or a structurally similar one. These data show that shared **epitopes** of human **melanoma** cells presented on HLA class II molecules are frequently recognized by autologous **CD4+** T lymphocytes.

L11 ANSWER 1 OF 34 MEDLINE
AN 96079058 MEDLINE
DN 96079058 PubMed ID: 7494321
TI **Binding** motifs **predict** major histocompatibility complex class II-restricted epitopes in the Sendai virus M protein.
AU Cole G A; Tao T; Hogg T L; Ryan K W; Woodland D L
CS Department of Immunology, St. Jude Children's Research Hospital, Memphis, Tennessee 38105, USA.
NC AI 31596 (NIAID)
AI 32529 (NIAID)
P30 CA21765 (NCI)
SO JOURNAL OF VIROLOGY, **(1995 Dec)** 69 (12) 8057-60.
Journal code: KCV; 0113724. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-U31956
EM 199601
ED Entered STN: 19960217
Last Updated on STN: 19980206
Entered Medline: 19960111
AB Major histocompatibility complex (MHC) class I ligand motifs have been defined for a number of class I molecules and have been successfully used to identify class I-restricted cytotoxic T-cell epitopes. In contrast, the relative degeneracy of sequence motifs in naturally processed MHC class II ligands has suggested that they may be of more limited use. Here, we use a **predicted** I-Ab ligand motif to identify antigenic **peptides** in the Sendai virus Enders strain matrix (M) protein. The entire coding sequence of the M protein was derived, and seven **peptide** sequences that contained the **predicted** I-Ab motif were identified. Analysis of I-Ab-restricted M-specific T-cell hybridomas for reactivity to these synthetic **peptides** identified two distinct epitopes. These data demonstrate that MHC class II motifs can be valuable in **predicting** T-cell epitopes.

TI The effects of changes at **peptide** residues contacting MHC class II T-cell receptor on antigen recognition and human Th0 cell effector function.

AU Lamb J R; Higgins J A; Hetzel C; Hayball J D; Lake R A; O'Hehir R E
CS Department of Biology, Imperial College of Science, Technology and Medicine, London, UK.

SO IMMUNOLOGY, **(1995 Jul)** 85 (3) 447-54.
Journal code: GH7; 0374672. ISSN: 0019-2805.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199511
ED Entered STN: 19951227
Last Updated on STN: 19951227
Entered Medline: 19951106

AB Cytokines can influence the selection of functional subsets (Th1 or Th2) of **CD4**+ T cells. However, quantitative changes in affinity of **peptide**/major histocompatibility complex (MHC) class II/T-cell receptor (TCR) interactions may alter antigen density and modulate T-cell effector function. The possibility exists to use **peptide** analogues to induce a partial signal to dissociate production of interleukin-4 (IL-4) and interferon-gamma (IFN-gamma) by T-helper type-0 (Th0) cells and, consequently, to regulate T-cell function. Based on **binding** assays and resolution of the crystalline structure of an influenza virus haemagglutinin **peptide** (HA 306-318) bound to the human MHC class II molecule DRB1*0101, we synthesized HA **peptide** analogues with amino acid substitutions **predicted** to modify either MHC class II/**peptide** density or TCR/**peptide** interactions. When we examined their antigenicity using cloned human Th0 cells, the analogues, in general, elicited a gradation in potency reflected by a reduction in both proliferation and cytokine production (IL-2, IL-4 and IFN-gamma). Although the analogue HA-R309 diminished IL-2 production, none of the analogues tested could selectively induce only IL-4 or IFN-gamma. Since, in general, the effector functions of the Th0 cells examined here were resistant to selective manipulation by the **peptide** analogues, this suggests that for some clones of chronically activated T cells modulation of selected functions may be difficult to achieve.

L11 ANSWER 4 OF 34 MEDLINE
AN 95407684 MEDLINE
DN 95407684 PubMed ID: 7545875
TI Experimental autoimmune insulitis. Induction by T lymphocytes specific for a **peptide** of proinsulin.
AU Griffin A C; Zhao W; Wegmann K W; Hickley W F
CS Department of Pathology, Dartmouth Medical School, Lebanon, New Hampshire 03756, USA.
NC NS 27321 (NINDS)
T32 AI 07363 (NIAID)
SO AMERICAN JOURNAL OF PATHOLOGY, **(1995 Sep)** 147 (3) 845-57.
Journal code: 3RS; 0370502. ISSN: 0002-9440.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199510
ED Entered STN: 19951026
Last Updated on STN: 19960129
Entered Medline: 19951017
AB Type I diabetes, an autoimmune disease that occurs in humans and animals, is characterized by the destruction of insulin-secreting islet beta-cells of the pancreas. Antibodies directed toward multiple islet protein can be detected before diagnosis of type I diabetes; however, the identity of the inciting autoantigen(s) that targets beta-cells for destruction has not been defined. Autorecognition of many self-proteins by **CD4**+ T lymphocytes is restricted by the products of class II immune response genes of the major histocompatibility complex (MHC), and in human type I diabetes such a MHC association has been described. The present study uses a rat MHC class II (RT1.Bl) **peptide binding** motif to **predict** potentially autoreactive **CD4**+ T cell epitopes in two key islet beta-cell constituents: the enzyme glutamic acid decarboxylase (GAD) and the insulin precursor hormone proinsulin (PI). Seventeen-amino-acid-long **peptide** fragments of GAD and PI containing the **binding** motif were synthesized and used to generate **peptide**-specific, MHC class II-restricted, **CD4**+ T cell lines. Once established, the T cell lines specific for rat islet GAD and PI were adoptively transferred to naive, MHC-compatible rats. At 10 days after transfer, insulitis had developed in rats receiving PI-specific T cells, whereas no insulitis was observed in pancreata of rats receiving GAD-specific T cells. Of particular interest is the finding that the pathogenic T cell epitope identified in PI spans the endogenous cleavage site between the B-chain and C-**peptide** of insulin. Moreover, the PI-specific T cells were able to react specifically with material produced in vitro by a rat insulinoma cell line. These results demonstrate that pathogenic T cell epitopes can be located in portions of molecules that are subsequently degraded during normal enzymatic processing. As PI is found highest concentrations in the beta-cells of pancreatic islets, it is possible that this molecule and not its individual degradation products (ie, insulin and C-**peptide**) might serve as an autoantigen in the pathogenesis of type I diabetes.

L11 ANSWER 8 OF 34 MEDLINE
AN 95154369 MEDLINE
DN 95154369 PubMed ID: 7531642
TI T cell recognition of hepatitis B and C viral antigens.
AU Jung M C; Diepolder H M; Pape G R
CS Medical Department II, Klinikum Grosshadern, University of Munich, Germany.
SO EUROPEAN JOURNAL OF CLINICAL INVESTIGATION, **(1994 Oct)** 24 (10) 641-50. Ref: 77
Journal code: EN3; 0245331. ISSN: 0014-2972.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199503
ED Entered STN: 19950322
Last Updated on STN: 19960129
Entered Medline: 19950313
AB The outcome of hepatitis B and C heavily depends on the appropriate virus specific T cell response. Both CD8+ and **CD4+** T lymphocytes do not recognize native viral proteins but processed **peptides** bound to MHC class I and class II, respectively. For therapeutical intervention aimed at T lymphocytes in chronic carriers as well as for the development of new vaccines, a precise identification of immunodominant epitopes, which can be recognized by a majority of patients, is necessary. Biological features of certain viral antigens have been partly characterized in animal models, but with the availability of modern molecular technology it is possible to extend these findings to the human system. The identification of anchor residues and motifs in **peptides**, which are essential for **binding** to certain MHC class I and class II molecules, allows the **prediction** of MHC allele-specific epitopes within viral proteins. By the use of synthetic **peptides** and vaccinia expression vectors, several epitopes for cytotoxic and helper T lymphocytes have been identified in HBV and HCV antigens. In HBV infection cytotoxic T lymphocytes recognize epitopes within the polymerase protein, the envelope protein and the nucleocapsid. In HCV cytotoxic epitopes have so far been identified within the nucleocapsid, E1, E2 and NS2. Since virus specific CD8+ T lymphocytes lyse virus infected cells in vitro and seem to play an important role for viral elimination in vivo, activation of virus specific effector cells may be achieved by immunizing chronically infected patients with the MHC-allele-specific **peptides**. Epitopes for **CD4+** T lymphocytes have been demonstrated in the majority of HBV- and HCV-proteins. Different subsets of **CD4+** T lymphocytes influence the course of infection by the production of lymphokines which either support antibody production by B cells or cellular antiviral effector mechanisms. In acute and chronic HBV infection the HBcAg/HBeAg-specific T cell response is closely correlated to viral elimination and the occurrence of anti-HBe- and anti-HBs antibodies. In HCV infection the **CD4+** T cell response appears to be more heterogenous, and better functional characterization of the **CD4+** response to immunodominant **peptide** epitopes in association with certain disease stages is required. Since T cell activation, the resulting effector functions and **binding** of the **peptide** to the HLA-molecule mainly depend on the **peptide** structure, viral

mutations leading to amino acid changes may contribute to T cell non-responsiveness or an inappropriate T cell response. (ABSTRACT TRUNCATED AT 400 WORDS)